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10/519,392

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Yann Guiavarch

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

KOSAR, AARON J

ART UNIT

PAPER NUMBER

1609

MAIL DATE

DELIVERY MODE

06/29/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/519,392

Applicant(s)

GUIAVARCH ET AL.

Examiner

Aaron J. Kosar

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 58-81 is/are pending in the application.
- 4a) Of the above claim(s) 74-81 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 58-73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 3/10/2005.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application
- ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on April 4, 2007, is acknowledged.

Claims 74-81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim.

Claims 1 and 58-73 are examined on their merits.

Claim Objections

Claim 1 is objected to because of the following informalities:

The phrase "below 0.6 by weight" appears to omit the unit of measure. Support in the specification suggests below about 0.6% by weight (page 13, ¶2). For the sake of compact prosecution the claims have been examined with the units of percent by weight.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pectin methyl esterase or *Bacillus* (*B. licheniformis* or *B. subtilis*) α -amylase adsorbed on glass beads, does not reasonably provide enablement for all combinations of enzyme with all filler combinations in all structural associations or the components (*e.g.* free/unbound versus ionic, nonionic, or covalent linkage). The specification does not enable any person skilled

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in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are generally drawn to a thermally resistant enzyme-based device comprising a hermetically-sealed container containing a dehydrated enzyme, and a filler. The claims are further limited by the dependent claims to require a first and/or second filler, including fillers comprising organic or inorganic filler, glass, metal, or silica beads; glass, metal, silica, or

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polymeric container; or bacterial, vegetal, animal, or fungal enzyme, including pectin methyl esterase or bacterial α -amylase. Thus, the claims taken together with the specification imply a much broader breath of the claims than is supported by the disclosure..

(3) The state of the prior art, (4) the predictability or unpredictability of the art, and (5) the relative skill of those in the art:

The state of the prior art is such that it is known that reducing mobility of an enzyme by tethering (adsorption, covalent linkage, etc; See WOODSON Abstract and col.7 (USPATENT No. 5,739,004)- PTO1449 3/10/2005.) or by dehydrating (including lyophilization, etc) stabilizes the enzyme for extended use (storage/retention or preservation/enhancement of activity) and/or for increased thermal resistance (elevated resistance to thermal denaturation); however, the effect of dehydrating and/or tethering has been studied *a posteriori* and only on a limited number of systems, including *Aspergillus oryzae* α -amylase/trehalose (Terebiznik, M.R., et al. Lebensm.-Wiss. U.-Technol. 1997, 30, 513-518), *Candida cylindracea* lipase/lactose (anhydrous, but not dry solid: Gentili, A., et al. Journal of Molecular Catalysis B: Enzymatic. 1997, 3, 43-49.); amino acyclase adsorbed on DEAE-Sephadex (Kirk-Othmer. "Enzyme Applications (Industrial)", Encyclopedia of Chemical Technology. 4th ed. vol.9, page 585.); and, commercially available active, substrate bound enzymes. In the context of thermal processing of starch, it is also known that α -amylase from *B.licheniformis*, *B.subtilis*, and *Aspergillus oryzae* have industrial importance, including *B.licheniformis* and *B.subtilis* α -amylases with activity above 80°C (Kirk-Othmer: page 598; table 4, page 599.)

However, given the diversity of enzymes and fillers available to one of skill - with a myriad of combination of the elements, each combination requiring separate handling and

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enzyme-/filler-specific optimal degree(s) of hydration for stability, and different structural elements affecting the drying and tethering process for each composition - it is does not appear to be established as to how one would predict *a priori* the effects (including magnitude of the change, amount of denaturation, etc.) of tethering or dehydrating processes on all enzymes and/or fillers.

Since the *a priori* selection of dried/lyophilized enzyme-filler pairs which have application within the range of 80-160°C remains largely unsolved, means for making and using an enzyme-filler-based device is highly unpredictable and thus beyond the purview of the skilled artisan.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided limited direction and guidance on how to make and use the invention as it pertains to pectin methyl esterase or *Bacillus* (*B. licheniformis* or *B. subtilis*) α -amylase and enzyme adsorption upon glass beads; however, the specification does not provide sufficient working examples and direction so as to be representative of the broad genus of dry enzyme or filler having utility as embraced by the claims.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed *supra* and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make and/or use the invention as claimed.

It is the Examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 59-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases “at least one first filler” and “at least one second filler” are indefinite because *first* and *second* imply singular, sequential entities. To the contrary, *at least one* includes multiple entities. It is unclear if the claims are drawn to a single first filler (and a single second filler) or if drawn to more than one (or two) enzymes. Each is a reasonable interpretation of the claims and each defines a different invention. It is unclear which invention Applicant intends to claim and thus one of skill would not be able to determine the metes and bounds of the subject matter embraced by the claims.

Claims 71-73 are indefinite for depending from indefinite claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 58, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by SEELICH (USPATENT No.4,816,251: PTO-892, 3/2/2007).

The claims are generally drawn to a thermally resistant enzyme-based device comprising a hermetically-sealed container containing a dehydrated enzyme, and a filler. Claim 58 adds the further limitation of claiming an organic filler.

Seelich as presented in the restriction requirement dated March 2, 2007, anticipates the above limitations by teaching a composition comprising: water content of 0.005 (0.5%) by

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weight of a composition comprising Factor XIII; Factor XII, an enzyme classified in EC 2.3.2.13; fibrinogen, an organic filler; a hermetically sealed container (column 6, lines 25-26; column 4, lines 46-48); and, heating to between 50 and 120°C, including 60 and 120°C.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 58-63, 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over MATNER (Matner, et al. USPATENT No.5,073,488) in view of KIRK-OTHMER (Kirk-Othmer. "Enzyme Applications (Industrial)", Encyclopedia of Chemical Technology. 4th ed. vol.9, page 584-620.) or DECORDT (DeCordt, Susanna F., et al. J. Chem. Tech. Biotechnol. 1994, 59, 193-199. – PTO 1449 3/10/2005) or CAMERON (Cameron, P.A., et al. Biotechnology and Bioengineering. 2002, 78(3), 251-6.)

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The claims are generally drawn to a thermally resistant enzyme-based device comprising a hermetically-sealed container containing a dehydrated enzyme, and a filler.

Matner teaches an enzyme-based device for monitoring sterilization efficacy (Abstract; col.1, ¶ 1). Matner also teaches a hermetically-sealed (liquid-impermeable, col.2) container, including polymers (col. 14); the operational range of steam and dry heat sterilizations (20-180°C (in reference to enzyme substrate parameters), column 6); exposure to thermal sterilization (121-135°C, col. 14); enzymes from *Bacillus*, *Clostridium*, *Neurospora*, and *Candida*, including *B.subtilis*, including one or more enzymes (column 6), including fillers (enzyme carriers: foil, beads, and fibers of paper, polymer, aluminum/stainless steel, glass, or porcelain and combinations thereof; col. 14) . Matner does not teach dehydrated enzyme mix, methyl esterases/bacterial α -amylases or low moisture.

Kirk-Othmer teaches that *B.licheniformis* and *B.subtilis* α -amylases are important thermostable industrial enzymes for heating processes in the range of 80-105 °C and up to 150°C (page 598; table 4, page 599) and useful in food processing as the source organism is considered as harmless contaminants of food (page 616). Kirk-Othmer also teaches advantages that immobilization of enzymes (page 584) has the benefit of reducing dust generation (page 615), resolution of catalyst from product, amplification of substrate versus enzyme (large substrate volume versus small reactors, including reuse of enzyme), and tuning of extent of enzymatic activity (adjusting flow rate)(page 584).

DeCordt teaches *B.licheniformis* α -amylase stabilized, including on glass beads (filler: "Carrier", page 194) for use as a time temperature integrator (a thermal impact

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monitor)(Introduction ¶3, page 193) and treated in a hermetically sealed container (crimp top vial, page 194). DeCordt does not teach a dried mix/low moisture.

It would have been obvious for one practicing the invention of Matner to use a *Bacillus* enzyme which is immobilized because DeCordt teaches a *Bacillus* amylase enzyme immobilized upon a glass bead.

One would have been motivated to use an immobilized enzyme because Kirk-Othmer teaches several advantages of using immobilized enzyme (see above) and DeCordt teaches that very often protein resistance to inactivation is improved with immobilization by a mechanism which adventitiously lowers the heat inactivation rate constant (DeCordt, page 193).

From the teachings of the references, one would have had a reasonable expectation of success in making a device comprising an immobilized enzyme, because DeCordt teaches that adsorption to glass beads of the amylase “can be met quite satisfactorily” with organic linkers such as “GA” and “TCTA” to bind the enzyme to the bead *and* reproducible in a linear relation to the concentration of enzyme applied to the enzyme (page 195).

The general teaching of CAMERON teaches that “drier enzyme is more stable at higher temperature” and that varying relative humidity (H_R) of immobilized enzyme effects its activity and stability (Introduction, page 251; Results, page 253). Cameron also teaches optimized values of 0.0% and 11.3% H_R (Table 1, page 252; page 253). It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions [e.g. material proportions or degree of dryness (the latter, dryness, by varying the sparge/spray dry gas stream *flow rate* and/or vary the pump’s (e.g. see page 253) *pressure/time/temperature*], because such conditions are art-recognized result-effective variables that are routinely determined and

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optimized in the art through routine experimentation. Furthermore, although Cameron does not teach the specifically claimed concentration of 0.6% water by weight, absent evidence to the contrary, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have optimized the concentration for percent water. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

From the teachings of the references, it is apparent that one of ordinary skill in the art Would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aaron J. Kosar whose telephone number is (571) 270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ajk/

Aaron Kosar

Examiner, Art Unit 1651


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